NOVARTIS

Clinical Trial Results Summary

A clinical trial to compare the effects and safety of different doses of brolucizumab with aflibercept in treating people with loss of vision due to Diabetic Macular Edema (DME)

Protocol number: CRTH258B2301

Thank You!

Novartis sponsored this trial and believes it is important to share what was learned from the results of this trial with the participants and the public.

Thank you for taking part in this trial for the drug brolucizumab, also known as RTH258. You helped researchers learn more about how brolucizumab works in people with Diabetic Macular Edema.

If trial participants have any questions about the trial results, please talk to the doctor or staff at the trial site.

This summary only shows the results of a single clinical trial. Other clinical trials may have different findings.

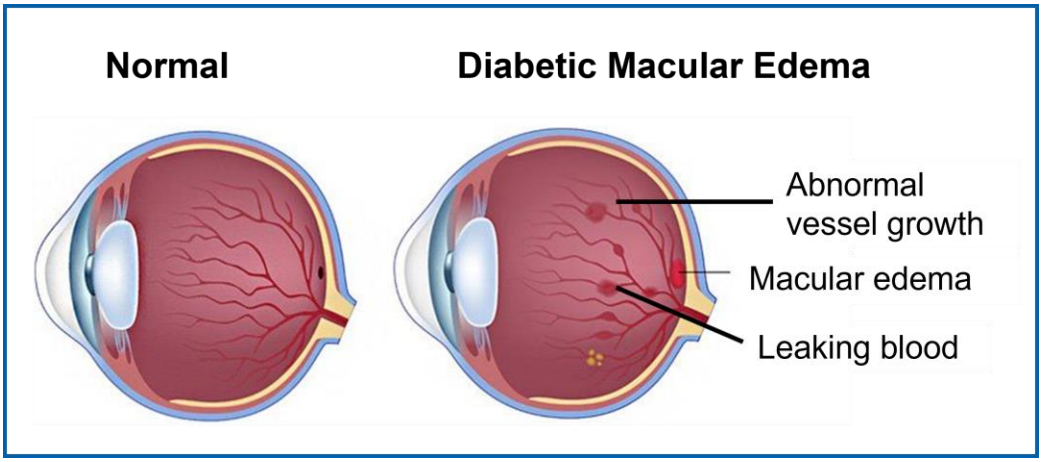
How long was this trial?

This trial started in July 2018 and ended in October 2021. The entire duration, from enrolling the first participant to the last participant completing the trial, was about 3 years and 3 months. An individual participant was in this trial for up to 2 years.

Why was the research needed?

Researchers were looking for a better way to treat participants with vision loss due to Diabetic Macular Edema (DME).

DME is the most common cause of vision loss in people with diabetes. In DME, there is swelling (edema) in the macula which causes fluid to leak from the damaged blood vessels of the retina. The retina is the part of the back of the eye that sends images to the brain. The macula is an area in the center of the retina that gives us sharp, clear vision. Over time, DME can cause vision to become blurred. Eventually, these changes can become permanent.



Source: EveryDayHealth.com

Currently, DME is treated with drugs such as aflibercept and ranibizumab. These drugs block a protein called vascular endothelial growth factor (VEGF) which causes abnormal growth and leakage of blood vessels at the back of the eye. Other treatments

include medicines called steroids, that reduce swelling, and laser treatments to stop blood vessels from leaking.

Drug	***Pronounced as***
Brolucizumab	*BRO-lu-SIZ-oo-mab*
Aflibercept	*a-FLI-ber-sept*
Ranibizumab	*RA-ni-BIZ-oo-mab*

Brolucizumab is the treatment being tested in this trial. This drug also blocks the protein called VEGF and, at the time of the trial, it had only been approved in some countries for another condition known as wet age-related macular degeneration.

In this trial, researchers wanted to know if vision test scores improved by a similar number in participants on brolucizumab compared to those on aflibercept by Week 52.

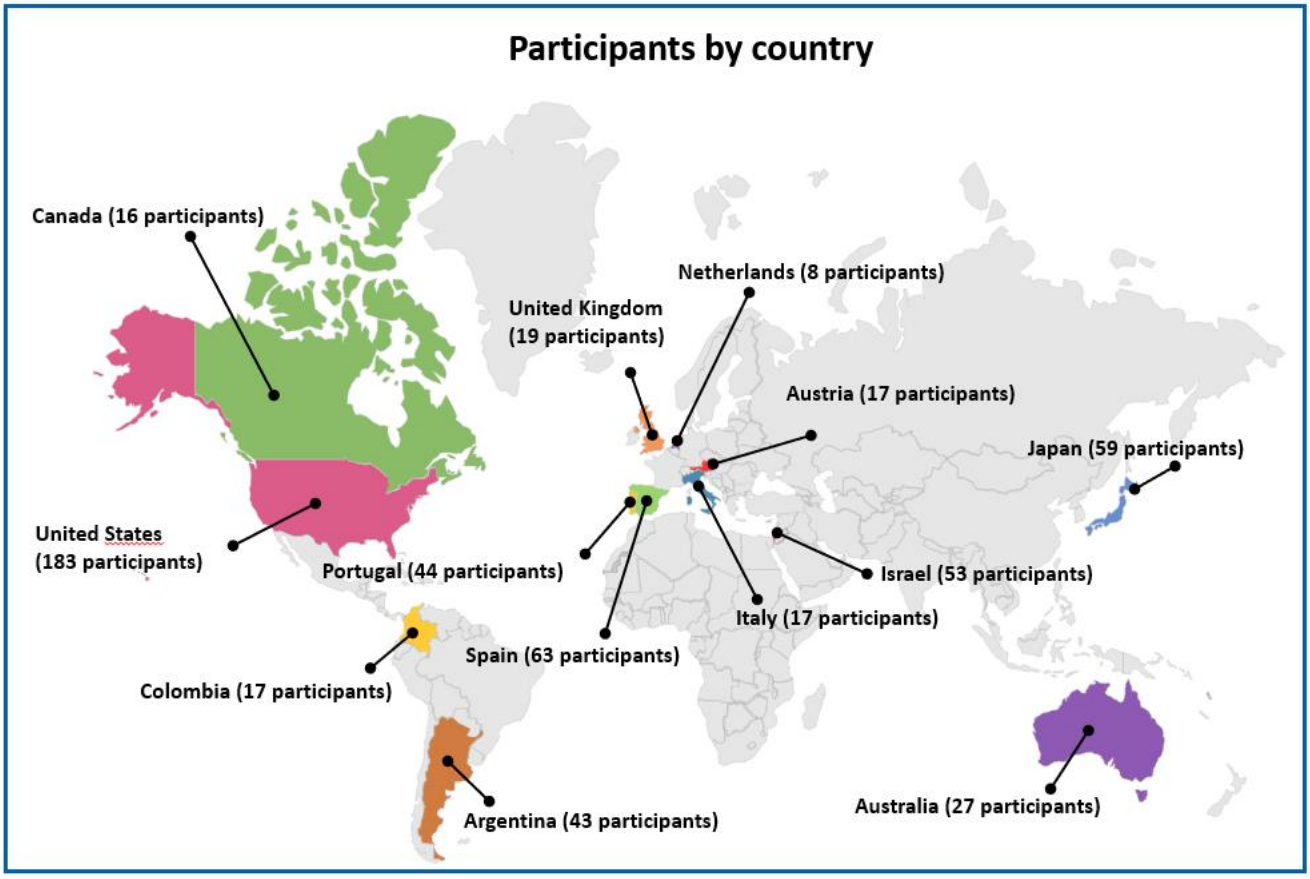
Who was in this trial?

The participants could take part in this trial if they:

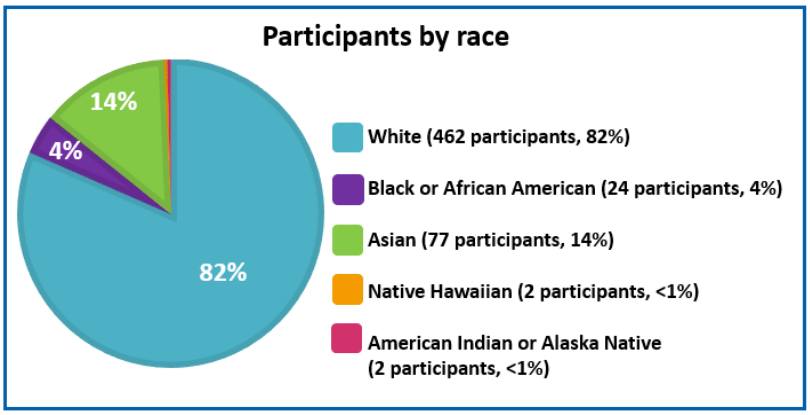
- were aged 18 years or older,
- had type-1 or type-2 diabetes,
- had DME, and could read at least 23 letters to 78 letters in the vision test, and
- did not have any other eye diseases that would impact trial participation.

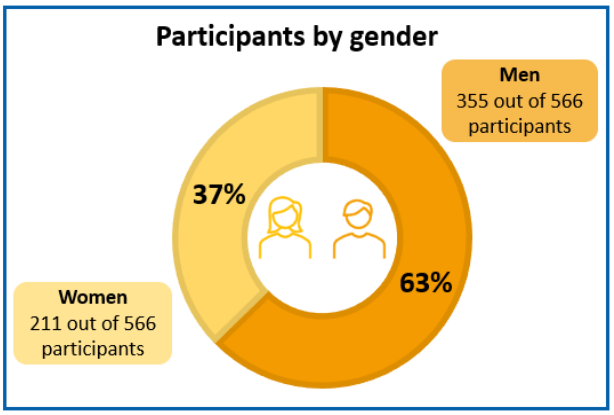
A total of 566 participants from 13 countries participated in this trial.

Participants were randomly assigned to treatment groups using a computer system. This process is called randomization. It means that each participant could be assigned to any group, and it helps to make sure the groups are distributed fairly.



The average age of participants was 64 years. Participants' age ranged from 23 to 87 years. Most participants were white men with type 2 diabetes.





What treatments did the participants take?

Study drug		Comparator drug	
	**Brolucizumab (3 mg and 6 mg)** is a drug that is not yet approved for the treatment of DME. It has been approved for the treatment of a similar condition known as wet age-related macular degeneration. It is given as an injection into the eye.		**Aflibercept 2mg** is a drug approved for the treatment of DME. It is given as an injection into the eye.

What happened during this trial?

Before treatment (screening)

- The trial doctors checked if participants could take part in this trial.
- Eligible participants were randomly assigned into one of the following 3 groups. Each participant had an equal chance of ending up in either group.

  Group 1: Brolucizumab 3 mg as an injection into the eye
  Group 2: Brolucizumab 6 mg as an injection into the eye
  Group 3: Aflibercept 2 mg as an injection into the ey

Up to 2 weeks

During treatment

Group 1: Brolucizumab 3 mg	Group 2: Brolucizumab 6 mg	Group 3: Aflibercept 2 mg
Once every 6 weeks until Week 24, and then once every 12 or 8 weeks (depending on the severity of the disease) until Week 96 (last treatment).		Once every 4 weeks until Week 16, and then once every 8 weeks until Week 96 (last treatment).
190 participants	**189 participants**	**187 participants**

- The drug was injected directly into the selected study eye. Participants did a vision test at every visit to the site. Researchers monitored the participant's health throughout the trial.

Up to 96 weeks

After treatment

- Participants had their end-of-trial visit 4 weeks after their last treatment.
- Researchers monitored the overall health of the participants throughout the trial and completed it as planned.

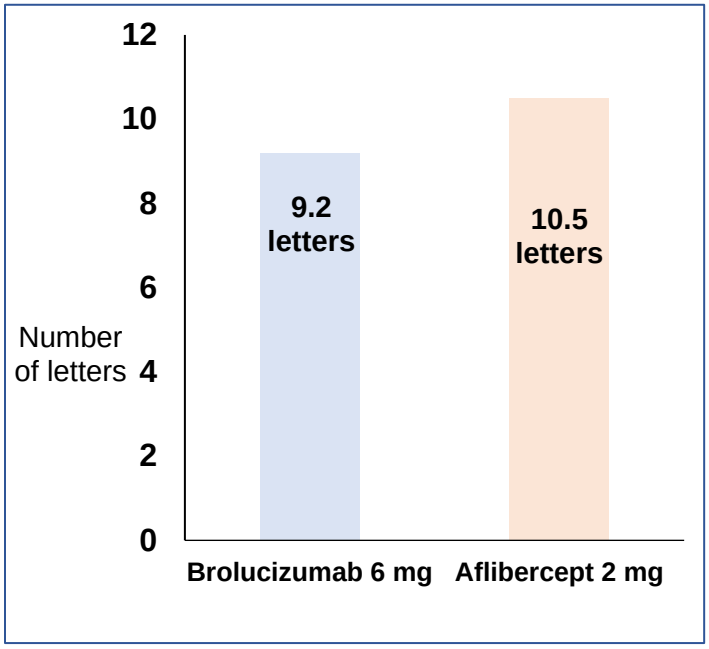
Up to 4 weeks after the last dose

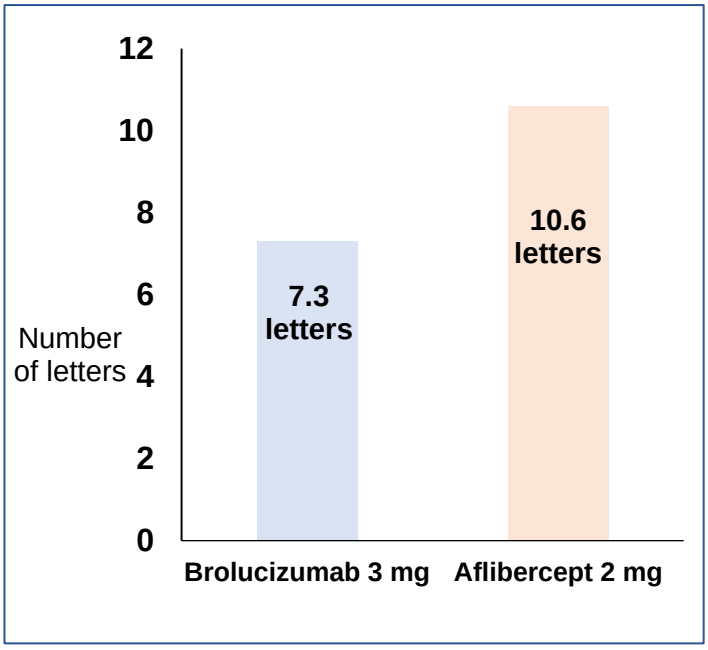
What were the main results of this trial?

Did vision test scores show similar improvement for brolucizumab 3 mg or 6 mg compared to aflibercept after 52 weeks of treatment?

Following 52 weeks of treatment, the improvement of vision in participants who received brolucizumab 6 mg was similar to participants who received aflibercept 2 mg. The improvement of vision in participants who received brolucizumab 3 mg was not similar to participants who received aflibercept 2 mg.

Improvement in vision test scores at week 52





What were the other results of this trial?

Did vision test scores show similar improvement for brolucizumab 3 mg or 6 mg compared to aflibercept 2 mg during and up to the end of the trial (Week 100)?

The average vision test scores showed similar improvement for participants who received brolucizumab 6 mg compared to those who received aflibercept 2 mg during and up to the end of the trial (Week 100). The average vision test scores were not similar for participants who received brolucizumab 3 mg compared to those who received aflibercept 2 mg during and up to the end of the trial (Week 100).

Did participants on brolucizumab 3 mg or 6 mg show a similar reduction in the thickness (swelling) of the central part of the retina compared to participants on aflibercept 2 mg at the end of the trial (Week 100)?

At the end of the trial (Week 100), on average, participants who received brolucizumab 3 mg or 6 mg showed a similar reduction in the thickness (swelling) of the central part of the retina compared to participants who received aflibercept 2 mg.

What medical problems did the participants have during the trial?

Medical problems that happen in clinical trials are called “adverse events”.

A lot of research is needed to know whether a drug causes an adverse event. During a trial, all adverse events are recorded, whether or not they are thought to be caused by the trial drug. When new drugs are being studied, researchers keep track of all adverse events participants have.

An adverse event is an unwanted sign, symptom, or disease that participants have during a trial.

An adverse event is considered “serious” when it is life-threatening, causes lasting problems, or the participant needs hospital care. These problems may or may not be caused by the trial drug.

This section is a summary of the adverse events that happened during this trial. The websites listed at the end of this summary may have more information about all the adverse events that happened in this trial.

How many participants had adverse events?

In this trial, researchers wanted to distinguish between ocular adverse events (adverse events of the eye) and non-ocular adverse events (adverse events not related to the eye). The number of participants with ocular or non-ocular adverse events is presented in the table below:

Number of Participants (%) With Ocular Adverse Events

Category	**Brolucizumab 3 mg** (190 participants)	**Brolucizumab 6 mg** (189 participants)	**Aflibercept 2 mg** (187 participants)
At least 1 adverse event	103 (54%)	92 (49%)	94 (50%)
At least 1 serious adverse event	8 (4%)	7 (4%)	5 (3%)
Stopped drug due to adverse event	7 (4%)	3 (2%)	2 (1%)

Number of Participants (%) With Non-Ocular Adverse Events

Category	Brolucizumab 3 mg (190 participants)	Brolucizumab 6 mg (189 participants)	Aflibercept 2 mg (187 participants)
At least 1 adverse event	146 (77%)	146 (77%)	143 (76%)
At least 1 serious adverse event	48 (25%)	53 (28%)	54 (29%)
Stopped drug due to adverse event	5 (3%)	2 (1%)	7 (4%)
Deaths	4 (2%)	8 (4%)	7 (4%)

What were the most common serious adverse events?

In this trial, researchers wanted to distinguish between the most common serious adverse events in the eye (ocular adverse events) and the most common serious adverse events in other parts of the body (non-ocular adverse events).

Ocular serious adverse events

The most common serious adverse events that happened in at least 1% (1 out of 100) participants in any group are shown below:

Number of Participants (%) With Most Common Ocular Serious Adverse Events

	Brolucizumab 3 mg (190 participants)	Brolucizumab 6 mg (189 participants)	Aflibercept 2 mg (187 participants)
Blood in the vitreous* - untreated eye (Vitreous haemorrhage – fellow eye)	2 (1%)	1 (<1%)	**0**
Clouding of the eye – treated eye (Cataract – study eye)	1 (<1%)	5 (3%)	3 (2%)
Clouding of the eye – untreated eye (Cataract – fellow eye)	0	3 (2%)	4 (2%)
Swelling of the retinal artery – treated eye (Retinal vasculitis – study eye)	2 (1%)	0	0

* Vitreous is a gel-like fluid that fills the eye

Non-ocular serious adverse events

The most common non-ocular serious adverse events that happened in at least 2% (2 out of 100) participants in any group were:

Number of Participants (%) With Most Common Non-Ocular Serious Adverse Events

	Brolucizumab 3 mg (190 participants)	Brolucizumab 6 mg (189 participants)	Aflibercept 2 mg (187 participants)
COVID-19 infection (COVID-19)	2 (1%)	3 (2%)	2 (1%)
Hardening of the arteries (Coronary artery disease)	1 (<1%)	2 (1%)	3 (2%)
Heart attack (Myocardial infarction)	2 (1%)	3 (2%)	3 (2%)
Heart failure (Cardiac failure congestive)	5 (3%)	2 (1%)	5 (3%)
Infection of the bone (Osteomyelitis)	1 (<1%)	2 (1%)	3 (2%)
Kidney failure (Renal failure)	1 (<1%)	1 (<1%)	4 (2%)
Stroke (Cerebrovascular accident)	3 (2%)	4 (2%)	4 (2%)
Worsening of diabetes (Diabetes mellitus)	0	3 (2%)	0

What were the most common non-serious adverse events?

Ocular non-serious adverse events

The most common ocular non-serious adverse events that happened in at least 5% (5 out of 100) of participants in any group are presented below:

Number of Participants (%) With Most Common Ocular Non-Serious Adverse Events

	Brolucizumab 3 mg (190 participants)	Brolucizumab 6 mg (189 participants)	Aflibercept 2 mg (187 participants)
Blood spots on the white part of the eye – treated eye (Conjunctival haemorrhage – study eye)	19 (10%)	16 (8%)	19 (10%)
Clouding of the eye – treated eye (Cataract – study eye)	17 (9%)	16 (8%)	13 (7%)
Difficulties in vision – treated eye (Vision acuity reduced – study eye)	7 (4%)	3 (2%)	9 (5%)
Dry eye – treated eye (Dry eye – study eye)	10 (5%)	6 (3%)	5 (3%)
Eye pressure increased – treated eye (Intraocular pressure increased – study eye)	14 (7%)	11 (6%)	3 (2%)
Separation of the vitreous* from the retina – treated eye (Vitreous detachment – study eye)	9 (5%)	10 (5%)	3 (2%)
Spots in vision due to shrinking of the vitreous* – treated eye (Vitreous floaters – study eye)	7 (4%)	10 (5%)	6 (3%)
Swelling in the back of the eye due to excess sugar that weakens the blood vessels of the eye – treated eye (Diabetic retinal oedema – study eye)	12 (6%)	9 (5%)	4 (2%)

* Vitreous is a gel-like fluid that fills the eye

Non-ocular non-serious adverse events

The most common non-serious adverse events that happened in at least 5% (5 out of 100) of participants in any group are presented below:

Number of Participants (%) With Most Common Non-Ocular Non-Serious Adverse Events

	Brolucizumab 3 mg (190 participants)	Brolucizumab 6 mg (189 participants)	Aflibercept 2 mg (187 participants)
Common cold (Nasopharyngitis)	20 (11%)	18 (10%)	16 (9%)
Cough (Cough)	7 (4%)	11 (6%)	10 (5%)
COVID 19 infection (COVID-19)	10 (5%)	10 (5%)	8 (4%)
Diarrhea (Diarrhoea)	5 (3%)	10 (5%)	6 (3%)
High blood pressure (Hypertension)	23 (12%)	20 (11%)	23 (12%)
Infection of the urinary system (Urinary tract infection)	17 (9%)	21 (11%)	8 (4%)
Joint pain (Arthralgia)	12 (6%)	6 (3%)	5 (3%)

How many participants stopped trial drugs due to adverse events?

Ocular adverse events

During the trial, 12 out of 566 (2%) participants stopped the treatment early due to ocular adverse events.

7 out of 190 (4%) participants stopped brolucizumab 3 mg early due to **swelling in the eye wall** (uveitis), **eye pressure increased** (Intraocular pressure increased),

abnormal wrinkling of the retina (epiretinal membrane), **detached retina** (retinal detachment), **swelling of the inner tissues of the eye** (iridocyclitis), **blockage of blood vessel carrying oxygen to the retina** (retinal artery occlusion), and **loss of vision due to high pressure inside the eye** (glaucoma).

3 out of 189 (2%) participants stopped brolucizumab 6 mg early due to i**nflammation of the eye** (eye inflammation), **swelling in the eye wall** (uveitis), and **swelling in the back of the eye due to excess sugar that weakens the blood vessels of the eye** (diabetic retinal oedema).

2 out of 187 (1%) participants stopped aflibercept 2 mg early due to i**nfection inside the eye** (endophthalmitis), **swelling and irritation in the eye** (iritis).

Non-ocular adverse events

During the trial, 5 out of 190 (3%) participants from the brolucizumab 3 mg group, 2 out of 189 (1%) participants from the brolucizumab 6 mg group, and 7 out of 187 (4%) participants from the aflibercept group stopped early due to non-ocular adverse events.

How was this trial useful?

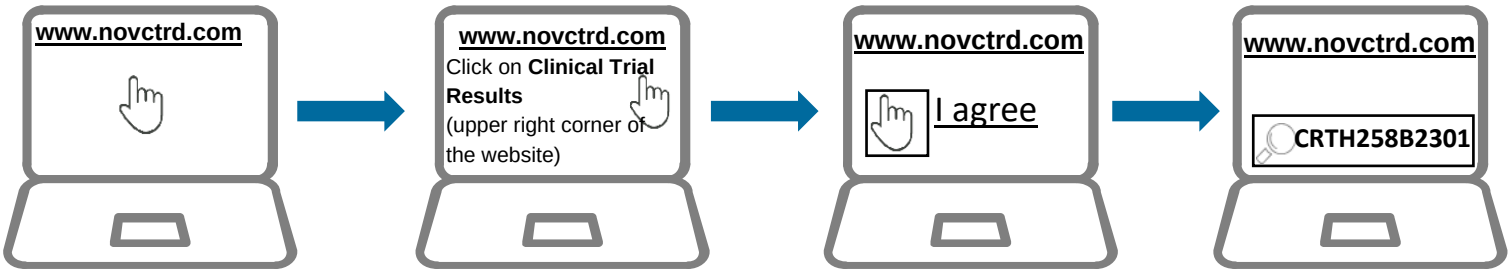
The trial helped researchers to learn about the effects and safety of brolucizumab 3 mg and 6 mg doses compared to aflibercept 2 mg in participants with vision loss due to DME. The results of this trial showed that brolucizumab 6 mg had similar effects to aflibercept 2 mg while brolucizumab 3 mg does not.

As a result of this trial and other clinical trials, brolucizumab 6 mg was approved for treating DME in the United States and several European countries.

Where can I learn more about this trial?

More information about the results and adverse events in this trial can be found in the scientific summary of the results available on the Novartis Clinical Trial Results website (www.novctrd.com).

Please follow the below steps:



You can find more information about this trial on the following websites:

- www.clinicaltrials.gov Use the NCT identifier NCT03481634 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search Use the EudraCT identifier 2017-004742-23 in the search field.

Full clinical trial title: A two-year, three-arm, randomized, double-masked, multicenter, phase III study assessing the efficacy and safety of Brolucizumab versus Aflibercept in adult patients with visual impairment due to Diabetic Macular Edema (KESTREL)

Thank you

Thank you for taking part in this trial. As a clinical trial participant, you belong to a large community of people around the world. You helped researchers answer important health questions and test new medical treatments.

NOVARTIS

Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide.

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